Intrahepatic cholestasis of pregnancy: Is fetoplacental doppler ultrasound useful in the diagnosis and follow-up?

Intrahepatic cholestasis of pregnancy

Veysel Toprak[1], Mehmet Tolga Kafadar[2]
[1]Tatvan Can Hospital Clinic of Obstetrics and Gynecology, Bitlis
[2]Department of General Surgery, Dicle University School of Medicine, Diyarbakır, Turkey

Abstract

Aim: In this study, we aimed to examine whether Doppler ultrasonography (USG) is an important diagnostic tool for fetal follow-up in case of obstetric cholestasis.

Material and Methods: This study included 50 patients diagnosed with obstetric cholestasis and 39 pregnant women turning up for their regular pregnancy follow-up. Pregnants were diagnosed according to definition, symptoms, and laboratory findings. Biochemical tests, bile acid test, upper abdominal USG, Non-Stress Test (NST), obstetric USG, amniotic fluid test, and fetoplacental Doppler USG were performed on all patients. Systole/Diastole (S/D) ratio of Umbilical artery (UA) and Middle cerebral artery (MCA)s, delivery types of patients, weight at birth, Apgar scores, and the existence of meconium were separately recorded.

Results: The mean age of the patients with obstetric cholestasis was 26.6 years, while in the control group it was 25.1 years (p = 0.176). No statistical difference was identified with regard to the average of (UA and MCA)/(S/D) ratio of both patient groups. In terms of delivery type, patients' UA and MCA S/D ratio averages were not statistically significant. There was no statistical link between cholestasis story in previous pregnancies, cholestasis in the current pregnancy, bile acid, and high ALP and baby's gender.

Discussion: Intrahepatic cholestasis of pregnancy is also a reversible form of cholestasis and it usually emerges in the late pregnancy period and continues until birth. In this study, it was detected that fetoplacental Doppler USG, which is used as a diagnostic tool for obstetric cholestasis, has a low level of predictivity. During our study, Doppler USG use in obstetric cholestasis diagnosis and follow-up was not effective.

Keywords

Cholestasis; Diagnosis; Doppler ultrasound; Fetal; Pregnancy

Introduction

Obstetric intrahepatic cholestasis is a disease that has high fetal morbidity and mortality rate, causes serious symptomatic illness for mother, and about the etiopathogenesis of which almost nothing is known. Since very little is known about etiopathogenesis, an obstetric approach to this clinical picture differs throughout the world. Since there was no precise pathogenic mechanism that can explain fetal morbidity and mortality until today, different diagnostic methods have been sought to be developed [1]. For the optimal development of the fetus during pregnancy the flow of fetal blood must be sufficient for placental villi, while the flow of maternal blood is adequate for intervillous space. In order to detect insufficiency of this flow, colour Doppler ultrasonography (USG), which is a non-invasive method, has been used in recent years. Doppler USG is a critical examination in terms of helping to find out which fetus requires closer follow-up [2]. In this study, it was aimed to examine whether Doppler USG is an important diagnostic tool for diagnosis and fetal follow-up in obstetric intrahepatic cholestasis.

Material and Methods

This study included 50 patients who applied to obstetric clinic in our hospital and were followed-up after hospitalization in perinatology service and diagnosed with obstetric cholestasis together with subsequent laboratory examinations, as well as 39 pregnants who visited hospital for routine pregnancy follow-up. Obstetric cholestasis was diagnosed according to symptoms (itching, hepatitis, etc.) and laboratory findings (high Alkaline phosphatase – ALP, Serum glutamic oxaloacetic transaminase – SGOT and serum glutamic pyruvic transaminase – SGPT). All patients complained about itching. Other liver disorders in patients were excluded. The other diseases which laboratory values may confuse with USG results were also excluded. Detailed anamnesis was obtained from 50 patients applying with itching complaint. Particularly cholestasis attack history from previous pregnancies, if any, was included into anamnesis. In this way, disease recurrence frequency was compared with current information. General physical and obstetric examinations of all cases were carried out. All cases were in the range of gestational weeks from 32 to 40. In order to accurately evaluate gestational week tests, again all cases were selected among those who were sure about last menstruation date and/or had late 1st trimester and early 2nd trimester biometric USG. Informed consents of patients were obtained. SGOT (AST – Aspartate aminotransferase), ALP, GGT (Gamma-Glutamyl Transferase), bile acid results of patients were recorded. The limit value for SGOT (AST) and SGPT (ALT) was identified as <50 u/l, for ALP it was <120 u/l, and for bile acid it was 10 mmol/l. Biochemical examinations were carried out in our hospital with standard methods by Cobacs C 501 model device of Hitachi brand (Roche, Turkey) and bile acid tests were carried out in external laboratory centres by KIT of Trinity Biotec brand. Upper abdominal USG was performed again on all cases in the radiology department of our hospital and the existence of a disease-specific or accompanying pathology was investigated. In order to evaluate fetal's well-being, Non-Stress Test (NST) (weekly), obstetric USG, and amnion fluid test along with fetoplacental

Doppler USG and bile acid tests, which constitute the basis of our study, were performed. Ultrasonographic evaluations were performed through the transabdominal method using 3.75 Mhz convex prob with Medison device. Umbilical arterial (UA) and middle cerebral artery (MCA) Systole/Diastole (S/D) ratios were separately recorded through the Doppler USG method. Since (UA) / (S/D) ratio is known to be < 3 and (MCA) / (S/D) ratio is known to be > 4 in the normal fetus, we comply with this standard in our study. Cases with birth weights less than 10 percentile were accepted as intrauterine growth retardation (IUGR), those with gestation age below 37 weeks were accepted as premature. And, thus, disease-specific premature rates were identified by again comparing to current data. Besides, all cases were clinically followed and delivery types, birth weights, 1 and 5 minutes Apgar values, and meconium existence and baby's sex were recorded.

With regards to 50 pregnants with obstetric cholestasis and 39 pregnants in the control group, detailed anamnesis records, laboratory results, cardiotocography (NST) scans, obstetric and Doppler USG tests, amniotic fluid tests, delivery type, weight at birth, Apgar and meconium existence and baby's sex were accepted and recorded as separate parameters and subsequently, fetoplacental Doppler USG and bile acid tests, which constitute the basis of our study, were performed. The relationship of Doppler USG and bile acid tests with fetal well-being was investigated. The study was planned in accordance with the decisions of the Helsinki Declaration, patient rights regulation, and ethical rules. Ethics committee approval was received for this study from the Ethics Committee of İzmir Ege Maternity and Gynecology Training and Research Hospital (12.05.2009 /2009-2- EPK).

Statistical Analysis

In statistical analyses, the Fisher's Exact Test, the Mann-Whitney U, and the Pearson Chi-Square Tests were performed. Data were in the form of average +SD and p<0,05 was accepted significant.

Results

Demographic data of 50 patients who applied to obstetrics clinic in our hospital with prevalent itching complaint, and subsequently after examinations diagnosed with "obstetric cholestasis" and of 39 patients in the control group were given in Table 1. While the mean age of patients with obstetric cholestasis was 26.6, the mean age for the control group was 25.1 (p=0.176). There was no statistical difference between the groups of gravid and parity (p= 0.258). Gestation week for patients with cholestasis was 37 weeks and there were a total of 17 (34%) patients with obstetric cholestasis and there were 15 (38%) patients in the control group. The average gestation age was 37.7 weeks for patients with obstetric cholestasis and 37.8 weeks for the control group. While the standard deviation was 1.49 for obstetric cholestasis patients, it was 2.49 for the control group. With regards to (UA and MCA) / (S/D) ratio average of patients distinguished according to gestation week, there was no statistically significant difference between the two groups. The preterm delivery rate, however, was 40%.

C-section rate for patients with obstetric cholestasis was 64% while it was found 49% in the control group (p>0.05). This rate

Table 1. The mean and standard deviation of demographic data of pregnant women with cholestasis and the control group

Group	Pregnant with cholestasis 50/SD	Control Group 39/SD
Age	26.68/5.63	25.15 /4.66
Gravida	1.72 /1.262	1.77 /0.902
Parity	0.52/0.974	0.74 /0.880
Live	0.40 /0.756	0.74 /0.880

SD: Standard Deviation

Table 2. SGOT and SGPT in pregnant women complicated by pregnancy cholestasis correlation of doppler means with values

Group	SGPT ≤50 U/L±SD	SGPT >50 U/L±SD	p-value
n (%)	40 (80)	10 (20)	
UA	2.97 ±1.144	2.25±1.149	0.020
MCA	3.74±1.790	4.33 ±1.642	0.216
	SGOT ≤50 U/L±SD	SGOT >50 U/L±SD	
n (%)	42 (84)	8 (16)	
UA	2.88 ±1.138	2.25±1.337	0.122
MCA	3.68±1.698	5.47±1.704	0.023

UA: Umbilical Artery, MCA: Middle Cerebral Artery, SD: Standard Deviatio

Table 3. Comparison of UA and MCA Doppler mean values according to NST findings in pregnancy cholestasis

Group	NST reactive ±SD	NST nonreactive ±SD	p
n / %	38/64	12/24	
UA	2.76±1.094	2.85±1.432	0.768
MCA	3.74±2.428	4.32±1.491	0.562

UA: Umbilical Artery, MCA: Middle Cerebral Artery, SD: Standard Deviation
NST: Non-Stress Test

is high compared to normal pregnant population (C-section rate of our hospital was 33% for the same period). C-section was performed on 25 out of 32 patients (78%) due to fetal distress and it was performed on 4 of them for elective purposes.

The birth weight of 90% of patients with obstetric cholestasis was within normal limits, while this percentage was 82% for the control group. In six cases (12%), weight at birth was under 2.500 gr., 5 out of these 6 cases were preterm delivery and 1 of them was diagnosed with IUGR.

There were a total of 16 patients who gave at least one birth before (out of 50 patients with obstetric cholestasis). Among these patients, 8 (16%) experienced cholestasis during their previous pregnancies. Doppler results of pregnants who experienced cholestasis during their previous pregnancies and Doppler results of other 42 pregnants who did not experience cholestasis in their previous pregnancies and control group were within normal limits. And the difference between them was not statistically significant.

Any increase in SGOT and SGPT values and any discrepancy in Doppler values were not identified. With the increase of SGOT and SGPT values, no discrepancy in Doppler values was detected. While p- value for SGOT-US was 0.122, p-value for

SGOT-MCA was 0.023, whereas p-value for SGPT-UA was 0.020, p-value for SGPT-MCA was 0.216 (Table 2). When SGPT value went beyond normal value, there was a slight increase in (UA MCA) / (S/D) ratio average; however this was found senseless statistically. Likewise, similar change also applies for SGOT, and it was not statistically significant. When SGPT and SGOT value rose above normal value, the meconium rate did not increase. Meconium was detected in 9 out of 50 patients (18%) within the scope of this study.

As hematological parameters of pregnants, Bleeding Time (BT), Clotting Time (CT) and Prothrombin Time (PT) values were all within normal values. GGT, another diagnostic parameter, was detected to be within normal limits.

In 12 out of 50 patients (24%), NST was found to be non-reactive, and in 38 (64%), NST was found to be reactive. In both groups, UA and MCA / S/D ratio averages were within normal limits; and a slight increase in the 2nd group's values was not found to be statistically significant. In patients with obstetric cholestasis, the impact of NST findings on Doppler could not be revealed (Table 3).

Among patients whose NST was non-reactive, meconium was observed in 4 cases; and meconium was observed in 5 patients out of 38 (13%) whose NST was reactive. Since meconium was observed in 9 out of 50 patients (18%), 33% value was found to be statistically significant. However, meconium was observed in 4 patients whose NST was non-reactive.

In USG performed on patients on the day they applied to the hospital, polyhydramnios was detected in only 1 case; and amnion fluid index (AFI) was identified to be 275 (74-240). Oligohydramnios (<60) was detected in 2 cases. Amnion fluids of other patients were within normal values. UA and MCA S/D ratio average of patients according to their delivery type was not statistically meaningful. Doppler USG was performed on all 50 patients and the results were assessed. While US S/D ratio was calculated >4 in 10 patients, 9 among the same patients had MCA S/D ratio <3.

Statistically, there was no association between cholestasis story in previous pregnancies, cholestasis condition in the current pregnancy, bile acid, and high ALP and baby's gender. Baby-girl does not trigger cholestasis. Only 1 baby was born with 5 Apgar score. ALP value was detected as >50 u/l in all 50 patients. These values were above normal for all patients >50 u/l.

Meconium was detected in 8 pregnants with cholestasis who took Ursofalk (Ursodeoxycholic acid) and in 1 pregnant who did not use it; and this was not found to be statistically significant. Likewise, the relation between high bile acid and meconium and the relation between bile acid and NST findings were not found to be statistically significant.

Discussion

Cholestasis or impaired bile flow is the most widely known and destructive manifestations of hereditary or vested liver disease [3]. Intrahepatic cholestasis of pregnancy is also a reversible form of cholestasis and it usually emerges in the late pregnancy period and continues until birth. Although quality of life for pregnant women impairs in the presence of symptoms such as itching, hepatitis, fat malabsorption, etc., the prognosis for

mother is good [4]. For optimal growth of fetus during pregnancy, the flow of fetal blood must be sufficient for placental villi while the flow of maternal blood is adequate for intervillous space. In order to identify the sufficiency of this flow, color Doppler USG, which is a non-invasive method, has been used in recent years. While examining uterine and umbilical arteries provides information about uteroplacental and fetoplacental perfusion, examination of fetal organs with Doppler is useful for demonstrating hemodynamic changes occurring in response to fetal hypoxemia [5].

Fetoplacental circulation is characterised by high flow and low resistance. With gestational progress in normal pregnancy, a progressive increase is observed in end-diastolic flow. As pregnancy age furthers, Pulsatile Index (PI), Resistance Index (RI) and Systole/Diastole (S/D) speed rate reduce in Doppler USG based on a decrease in vascular resistance. This tertiary system reflects an increase in the number of villus and progressive maturation of the placenta. Umbilical-placental vascular expansion occurs and therefore vascular resistance decreases [6].

Pathological changes in umbilical artery take place with at least 60% obstruction of placental vascular bed. In this case, resistance increases and leads to diastolic decrease; and thus PI, RI, and S/D increase. Detection of abnormal Doppler findings in umbilical artery demonstrates that perinatal prognosis is negatively affected. Repeated tests give us further information. Observing an increase in S/D rate in repetitive tests carried out in progressive gestation weeks is more related with birth weight and bad perinatal results compared to single test. In repetitive tests, near-normal S/D rate is associated with good perinatal result [7].

Clinical value of umbilical Doppler studies lies in the fact that they help identify which foetus requires closer observation. However, it is obvious that only results of umbilical artery do not provide us sufficient information about when the fetus will be delivered and it must be evaluated with other diagnostic tests such as assessment of fetal development together with biophysical profile [8].

MCA end-diastolic flow used to evaluate fetal cerebral circulation is low up to 28-32 weeks and resistance indices are high. From this week to term, decrease in resistance in cerebral circulation and increase in average flow rate is observed. MCA is parallel with Doppler pulse in particular with its outrun form. Since Doppler angle is low, this artery provides easier and good signals compared to anterior and posterior cerebral arteries. It is possible to work with an angle close to zero degree between ultrasound and flow speed rate. Since it provides insight about brain sparing effect, it is the vein preferred to evaluate fetal cerebral circulation [9-11].

In 20% to 60% of patients having itching complaint and whose bile acid increased, transaminases elevate 2-10 times. In our study, there were 10 patients whose SGPT value was > 50 U/L (20%). While the highest SGPT value is 611 U/L, the highest SGOT value was 234 U/L. Since SGPT (ALT) is the most sensitive test among standard liver function tests, it is reasonable that SGPT demonstrates higher values [12, 13]. In our study, we also compared normal and over-normal values of SGOT and SGPT and UA and MCA S/D rates. Although there was a slight increase in both, this remained within normal values and it was found statistically senseless.

In a study conducted by Zimmermann et al. [14], UA PI indices and ALT (SGPT) values of 15 patients with obstetric cholestasis were compared and no correlation was provided between Doppler findings and weight of cholestasis as clinical findings. SGPT's normal and high values were compared with meconium; however, no statistical difference was detected here, either.

Since Doppler value alone is insufficient to assess fetal sequence, biophysical profile should also be included in assessment. As a result of weekly NST performed on our patients, non-reactivity was detected in 12 patients and 4 of them had meconium. This was not statistically significant. When Doppler values of those with reactive and non-reactive NST are compared, statistical senselessness emerges again, which shows that Doppler values do not constitute a correlation with biophysical parameters. In spite of the use of biophysical profile and Doppler, babies may die [15].

Premature rates in obstetric cholestasis vary from 19% to 66% [16, 17]. In our study, this rate was determined to be 34%. Average gestation week of patients was calculated as 37.4. Despite increased premature rate, babies were born at weights in compliance with gestation week. In Doppler average comparisons conducted according to gestation weeks, it was observed that there was no correlation.

In the literature, there are publications asserting that meconium causes acute umbilical vein construction and decrease in umbilical flow [18]. And yet, we could not establish any value in this regard with Doppler data we obtained. Parameters regarding clotting were found out to be normal in all patients. Besides, no post-partum bleeding was observed in any patient. Therefore, these criteria were not discussed, but since in the literature there are fetal death statements based on the impairment of these parameters, it is necessary to closely follow-up patients in this regard [19, 20]. Although ALP values are high in most patients with cholestasis, they are of weak prognostic importance [21]. In our study, ALP values varied from 168 to 524 U/L.

Obstetric cholestasis was not actually diagnosed until the 1950s. And it is a significant disease which importance particularly for fetus was not fully comprehended although it was diagnosed after the 1950s. Although the impact of this disease upon pregnant is only a symptomatic disturbance, it can be mortal for fetus. In general population, Doppler USG's use for scanning purpose only is not appropriate. Besides, it is difficult to decide delivering a baby only with the results of Doppler USG. In addition, modified biophysical profile and assessment with NST are required. Furthermore, since sudden fetal deaths are notified despite close clinical follow-up of obstetric cholestasis, apart from these, several laboratory tests (serum bile acid, serum and urinary progesterone metabolites tests) and even molecular genetic tests must be performed [22-24].

By taking averages of fetoplacental Doppler USG tests that we applied in our study, they were compared with laboratory tests (SGPT test which is a high diagnostic criterion for patients with obstetric cholestasis, SGOT, bile acid and ALP) and tests regarding foetus (gestation week, NST, delivery type, sex,

ursodeoxycholic acid use) and also the existence of cholestasis in patient's previous pregnancies; and yet no sensible rate with any of them could be determined. Even further, almost all Doppler data obtained remained within normal limits.

Conclusion

It is observed that fetoplacental Doppler USG, which is today used as an important diagnostic tool in obstetric cholestasis cases, only has a weak predictivity in correlation with today's literature information. According to this, in the light of recent studies, use of Doppler USG in close follow-up of this very critical clinical profile is not effective. Instead, serum bile acid and serum – urinary progesterone metabolites tests appear to be more sensitive in diagnosing this clinical profile.

References
1. Palmer KR, Xiaohua L, Mol BW. Management of intrahepatic cholestasis in pregnancy. Lancet. 2019;393(10174):853-4.
2. Zhang K, He J, Dong M. Relationship between umbilical artery Doppler waveform analysis and perinatal prognosis in women with intrahepatic cholestasis of pregnancy. Int J Gynaecol Obstet. 2010;111(2):187-8.
3. Lammert F, Marschall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J Hepatol. 2000;33(6):1012-21.
4. García-Romero CS, Guzman C, Cervantes A, Cerbón M. Liver disease in pregnancy: Medical aspects and their implications for mother and child. Ann Hepatol. 2019;18(4):553-62.
5. Wood AM, Livingston EG, Hughes BL, Kuller JA. Intrahepatic cholestasis of pregnancy: a review of diagnosis and management. Obstet Gynecol Surv. 2018;73(2):103-9.
6. Guerra F, Guzmán S, Campos G. Evaluation of maternal and fetal blood flow indices in intrahepatic cholestasis of pregnancy. Rev Chil Obstet Ginecol. 1994;59(1):17-21.
7. Bustos JC, Paublo M, Ramirez P, Sepulveda W. Umbilical artery half peak systolic velocity deceleration time throughout pregnancy and its role in fetuses with bradycardia. Ultrasound Obstet Gynecol. 2007;30(7):952-7.
8. Paublo MA, Aitken S, Atala C. Usefulness of the modified fetal biophysical profile in intrahepatic cholestasis of pregnancy. Rev Chil Obstet Ginecol. 1987;52(5):296-303.
9. Chacko KR, Wolkoff AW. Intrahepatic cholestasis of pregnancy: new diagnostic insights. Ann Hepatol. 2017;16(2):176-8.
10. Herrera CA, Manuck TA, Stoddard GJ, Varner MW, Esplin S, Clark EAS, et al. Perinatal outcomes associated with intrahepatic cholestasis of pregnancy. J Matern Fetal Neonatal Med. 2018;31(14):1913-20.
11. Lin J, Gu W, Hou Y. Diagnosis and prognosis of early-onset intrahepatic cholestasis of pregnancy: a prospective study. J Matern Fetal Neonatal Med. 2019;32(6):997-1003.
12. Kenyon AP, Tribe RM, Nelson-Piercy C, Girling JC, Williamson C, Seed PT, et al. Pruritus in pregnancy: a study of anatomical distribution and prevalence in relation to the development of obstetric cholestasis. Obstet Med. 2010;3(1):25-9.
13. Ma K, Berger D, Reau N. Liver Diseases During Pregnancy. Clin Liver Dis. 2019;23(2):345-61.
14. Zimmermann P, Koskinen J, Vaalamo P, Ranta T. Doppler umbilical artery velocimetry in pregnancies complicated by intrahepatic cholestasis. J Perinat Med. 1991;19(5):351-5.
15. Madazli R, Yuksel MA, Oncul M, Tuten A, Guralp O, Aydin B. Pregnancy outcomes and prognostic factors in patients with intrahepatic cholestasis of pregnancy. J Obstet Gynaecol. 2015;35(4):358-61.
16. Çelik S, Çalışkan CS, Çelik H, Güçlü M, Başbuğ A. Predictors of adverse perinatal outcomes in intrahepatic cholestasis of pregnancy. Ginekol Pol.
2019;90(4):217-22.
17. Gabzdyl EM, Schlaeger JM. Intrahepatic cholestasis of pregnancy: a critical clinical review. J Perinat Neonatal Nurs. 2015;29(1):41-50.
18. Menżyk T, Bator M, Derra A, Kierach R, Kukla M. The role of metabolic disorders in the pathogenesis of intrahepatic cholestasis of pregnancy. Clin Exp Hepatol. 2018;4(4):217-23.
19. Floreani A, Gervasi MT. New Insights on Intrahepatic Cholestasis of Pregnancy. Clin Liver Dis. 2016;20(1):177-89.
20. Lee RH, Kwok KM, Ingles S, Wilson ML, Mullin P, Incerpi M, et al. Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. Am J Perinatol. 2008;25(6):341-5.
21. Ozkan S, Ceylan Y, Ozkan OV, Yildirim S. Review of a challenging clinical issue: Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2015;21(23):7134-41.
22. Marschall HU. Management of intrahepatic cholestasis of pregnancy. Expert Rev Gastroenterol Hepatol. 2015;9(10):1273-9.
23. Kawakita T, Parikh LI, Ramsey PS, Huang CC, Zeymo A, Fernandez M, et al. Predictors of adverse neonatal outcomes in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol. 2015;213(4):570.e1-8.
24. Reyes H, Sjövall J. Bile acids and progesterone metabolites in intrahepatic cholestasis of pregnancy. Ann Med. 2000;32(2):94-106.